Treatment of Clinical Hypothyroidism With Thyroxine and Triiodothyronine: A Literature Review and Metaanalysis

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Thyroxine is the standard replacement therapy for patients with clinical hypothyroidism. However, there has been recent interest in examining the potential advantages of combined thyroxine and triiodothyronine treatment for the treatment of hypothyroidism. The authors review the nine studies to-date and conclude that the variability and limitations in study design make definitive and clinically useful recommendations difficult. They therefore conducted a metaanalysis of the nine controlled studies examining the impact of combined thyroxine-plus-triiodothyronine versus thyroxine alone, with measures of psychiatric symptoms as the primary outcome. Their analysis reveals no significant difference in treatment effect on psychiatric symptoms in the nine controlled studies to date. (Psychosomatics 2007; 48:379–384)

At present, T4 is the standard thyroid hormone used for replacement therapy for patients with hypothyroidism.[1,2] The endpoint of treatment is a stable, euthyroid state, defined by a normal circulating thyrotropin (TSH) level.[1]

Although the use of T4 has been the accepted standard of care for many years,[1] there are several lines of evidence that have prompted a reevaluation of the potential benefit of combined T4 and T3 treatment as replacement therapy for hypothyroidism. First, in most patients, the dose of T4 required to normalize TSH may be supraphysiological, producing slightly elevated circulating T4 levels.[3] Under normal physiological conditions, the majority of circulating T3 is derived from the peripheral deiodination of T4, although a small amount, approximately 20%, of the T3 is directly secreted by the thyroid gland. It is possible that with replacement therapy, where all the T3 is derived from peripheral conversion of T4, excess amounts of T4 are required to normalize TSH. The absence of endogenous T3 production from the thyroid gland may be of physiological significance.[3] Second, despite normalization of TSH as a target of treatment, a substantial minority of hypothyroid subjects on T4 replacement complain of various symptoms of depression and malaise and, consequently, reduced quality of life.[4] Clinical hypothyroidism may present with various psychiatric symptoms, including depression, and T4 replacement therapy producing normal TSH levels may not completely produce a euthyroid state in all organs and tissues.[3] Third, several open and controlled studies suggest that T3 may enhance response to antidepressants in depressed patients with no evidence of hypothyroidism. These studies indicate that the addition of small amounts of T3 may either augment or accelerate response to antidepressants in patients with primary major depressive disorder.[5] The role of T4 in promoting antidepressant response is still a matter of debate,[6] but T3 is more commonly used for this purpose. Last, animal studies have suggested that T4 replacement in thyroidectomized rats has a variable effect on different tissues and organs and does not necessarily produce a euthyroid state uniformly in all tissues (reviewed in Escobar-Morreale[3]). This implies that although the pa-

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tient may be euthyroid as defined by circulating thyroid hormone levels, particularly TSH, symptoms may arise from the uneven effect of T4 replacement therapy on various tissues and organs or even regions within the brain.

From a practical clinical perspective, the goal of thyroid hormone replacement therapy is to achieve normal premorbid physical, psychological, and cognitive functioning in the hypothyroid patient. Although levothyroxine is standard therapy, it is well recognized that a subset of patients are dissatisfied with the therapeutic impact of levothyroxine replacement. For example, Saravanan et al.[4] reported that 961 patients on levothyroxine therapy for a minimum of 4 months showed a statistically significant impairment in psychological well-being as compared with control subjects. Although the percentage of patients dissatisfied with levothyroxine therapy in general practice is unknown, it is a syndrome well recognized both by primary-care physicians[7] and endocrinologists,[8] and it is one of the driving forces behind the recent burst of articles evaluating the impact of T4 and T3 therapy.

In the last 6 years, there have been nine controlled studies that have examined the effect of combined T4-plus-T3 versus T4-alone on mood, cognitive, and endocrine parameters as replacement therapy for hypothyroidism. Eight of these studies have been published, and all are summarized in Table 1. The importance of this line of research is underscored by the relatively large number of studies to date and reflects the fact that hypothyroidism is a relatively common disorder in the United States population. Consequently, a large number of patients require replacement treatment, making the determination of optimum treatment a high clinical priority.[9] Moreover, the potential difference in effect of combined T4-plus-T3 versus T4-alone on psychiatric and cognitive measures may have important implications for further understanding the role that thyroid hormones may have in mood regulation and in the pathophysiology of mood disorders.[5,6]

We therefore aim to provide a critical review of these studies to further evaluate their potential clinical and theoretical implications. Furthermore, we have performed a metaanalysis of the nine studies to assess whether we could determine a more robust effect on mood and/or cognition of the combined treatment, as compared with T4-alone when the nine studies were considered together.

Literature Review

Nine studies, all of which used randomized, double-blind, placebo-controlled designs, were included (Table 1). In the first published study, Bunevicius and colleagues[10] studied 33 subjects with hypothyroidism on usual replacement therapy with T4. They used a crossover design so that each subject received 5-week treatment periods of either their usual T4 dose or the usual dose of T4, reduced by 50 μg per day and replaced by 12.5 μg of T3, in randomized order. Among the multiple mood and cognitive measures assessed, the combination treatment produced significant improvements as compared with T4 alone on most of these measures. As expected, circulating T4 levels were lower and T3 levels higher in the combination-treatment group, but TSH levels were comparable in the two groups. The authors concluded that the combination treatment had advantages over T4 alone and that the T3 secreted directly by the thyroid gland must have a physiologically significant role.

This study had several limitations, including a rela-

TABLE 1. Controlled Studies Examining Effect of Combined T4-plus-T3 Versus T4-Alone as Replacement Therapy for Hypothyroidism

Study	Design	Sample Size	Treatment Duration, weeks
Applehof et al.[16]	Double-blind, parallel	T4: 48 T4 + T3 (10:1): 46 T4 + T3 (6:1): 47	15
Bunevicius et al.[10]	Double-blind, crossover	33	5
Clyde et al.[11]	Double-blind, parallel	T4: 22 T4 + T3: 22	16
Escobar-Morreale et al.[3]	Double-blind, crossover	26	8
Levitt et al. (unpublished)	Double-blind, parallel	T4: 16 T4 + T3: 20	36
Sawka et al.[13]	Double-blind, parallel	T4: 20 T4 + T3: 20	15
Saravanan et al.[17]	Double-blind, parallel	T4: 353 T4 + T3: 344	52
Siegmund et al.[14]	Double-blind, crossover	23	12
Walsh et al.[12]	Double-blind, crossover	101	10

tively small sample size, the crossover design, and a short duration of treatment, which made it difficult to control for carry-over effects, which are of particular importance because T4 has a half-life of approximately 5 days. Nonetheless, the generally robust findings on mood and cognitive measures and the observation that most patients preferred combined treatment prompted further study of this issue.

Clyde et al.[11] conducted a parallel-design study over 4 months in 46 subjects on a military base. Half were assigned to T4 and the other to T4 reduced by 50 μg and substituted with 7.5 μg of T3. Quality-of-life and cognition were the primary outcome measures. Although there were no significant differences in outcome between the two groups, both improved with treatment across most measures. There was no evaluation of patient preference with regard to treatment.

Walsh and colleagues[12] used a crossover design where 101 hypothyroid subjects completed 10 weeks each of treatment with the usual T4 doses and with the T4 reduced by 50 μg and replaced by 10 μg of T3. There was a 4-week washout period. On a comprehensive battery of mood, cognitive, and quality-of-life measures, the two groups did not differ significantly, and subjects did not indicate any preference for either of the treatments. In addition to the crossover design, these findings are limited by the fact that the combination treatment produced significantly higher mean TSH levels than the T4 treatment, raising the possibility that relative undertreatment with combination therapy may have biased against a positive finding. In our own study,[13] we used a parallel design with up to 15 weeks of treatment. Patients were selected if they had a minimum level of depressive symptoms in the absence of a major depression, and 20 each were assigned either to their usual dose of T4 or to combination treatment, where the dose of T4 was reduced by 50% and substituted with 25 μg of T3. No significant differences occurred in any of the outcome measures in the two groups. Patient preference was not assessed.

Saravanan et al.[17] conducted by far the largest study, enrolling 697 hypothyroid subjects in a year-long, parallel-treatment design. Assessments were conducted at 3 and 12 months. A significant difference in improvement on mood measures in favor of combined treatment was observed at 3 months but was not sustained at 1 year. Combined treatment involved substitution of 50 μg of the usual dose of T4 with 10 μg of T3. Patient preference was not assessed. The authors concluded that combination treatment did not appear to offer clinical advantage over usual T4 monotherapy.

Siegmund et al.[14] performed a crossover study with two 12-week treatment periods and no intervening washout in 23 subjects, where 5% of the T4 dose was substituted with T3 in the combination phase. No significant differences were noted in mood, quality of life, and endocrine measures between treatments, and patient preference was not assessed.

Escobar-Morreale and his group[15] also used a crossover design, with 8-week treatment periods, in 28 hypothyroid women. They argued that combination therapy in the previous studies produced variable ratios of T4 to T3 that did not approximate the normal physiological ratios observed in healthy, euthyroid subjects. Using doses of T3 substitution to produce fixed T4-to-T3 ratios, they could not demonstrate significant advantages for combination therapy on any measure, although subjects did express a preference for combined treatment. In a similar vein, Appelhof et al.[16] compared usual doses of T4 with two combination groups, one producing a T4:T3 ratio of 10:1 and the other a ratio of 5:1.Treatment was administered in a parallel design for 15 weeks. The primary outcome measure was patient satisfaction with treatment, and the two combination-treatment groups had a significant advantage over T4 alone, but there were no significant difference in any of the secondary psychiatric measures. In the unpublished study of one of the authors (AJL), a parallel design was used to compare T4-alone with T4 + T3 given in a 15:1 ratio, assuming a biopotency of either 4:1 or 2.5:1. Forty-one subjects completed the 9-month follow-up. No differences in mood, cognition, or quality of life were noted between the three groups at baseline, but the combination treatments did result in greater improvement in residual symptoms of hypothyroidism. All treatment groups did improve, and patient preference was not assessed.

The review of these controlled studies produces inconclusive findings. Although most studies do not demonstrate robust differences between treatment groups, some important findings should be noted. In particular, in the four studies where patient preference for treatment was assessed, three[10,15,16] report patient preference for combination treatment, and only one reports no preference for treatment type.[12] Also, most studies have small sample sizes, short duration of treatment, and a crossover design, making interpretation of specific treatment effects difficult, and variable ratio of T4:T3 with the combination regimens of T4 + T3 used. With regard to the latter issue, attempts to control for a fixed T4:T3 ratio often introduced other issues, such as the suppression of TSH and potential deleterious effects on bone.[15,16] It should also be noted that

although, overall, there were not robust differences between treatments in most studies, aside from the issue of patient preference, individual tests or groups of tests measuring aspects of mood and cognition were significantly different between treatment groups (see Table 1). As a result, we decided to perform a metaanalysis of the outcome of these nine studies, as well as a sub-analysis of the four crossover studies where patient preference for type of thyroid hormone treatment was assessed.

METHOD

Given the relatively small number of studies, we applied summary statistics without formal statistical inferential tests. Because the studies often did not use identical measures of depression, but, rather, similar and comparable measures, standardized effect sizes, defined as mean differences between treatment and control groups standardized by the pooled standard deviation (SD),[19] were obtained for each study. To estimate overall effect size, we obtained the weighted average of these differences.

RESULTS

Details of the metaanalysis are outlined in Table 2. The overall weighted average of effect sizes is –0.011, indicating an overall nonsignificant difference in effect of treatment conditions across the included studies. Table 3 summarizes studies that included patient preference for thyroid hormone treatment. The outcome variable was patients' preference for T4-alone or combined T4 + T3. Appelhof et al.[16] did not report on "no-preference" versus "preference" as an outcome, even though patient preference was their primary outcome measure. They also compared the patients' current treatment with standard treatment, whereas the other studies gave subjects a choice of preference or no-preference for T4-alone or combined T4 + T3. The Appelhof et al.[16] study may not, therefore, be directly comparable to the other studies, but regardless of whether it is included or not, the overall percentages are similar across all studies (see Table 3). If the Appelhof et al.[16] study is excluded, there is a statistically significant trend from no-preference to single to combined treatment ($p<0.001$). Furthermore, there is a statistically significant difference in the overall percentages for preference for T4 versus T4 + T3 ($p = 0.03$).

DISCUSSION

In our review, nine controlled studies have not conclusively shown that the combination of T4 and T3 has substantial clinical benefit over T4-alone as replacement therapy for hypothyroidism. The limitations of individual studies, including generally small sample sizes, prompted us to per-

TABLE 2. Details of the Parameters of the Metaanalysis of Nine Controlled Studies Comparing T4 + T3 With T4-Alone for Replacement Therapy for Hypothyroidism

Study	Outcome Measure	Mean (SD) T4 / T4 + T3	Pooled SD T4 + T3 / T4	Effect Size
Appelhof et al.[16]	Profile of Mood States, Depression subscale	5.1 (6.5) 3.8 (4.4)	5.55	0.23
Bunevicius et al.[10]	Profile of Mood States, Depression subscale	13.4 (9.5) 10.5 (8.9)	9.20	0.31
Clyde et al.[11]	Quality of Life	58 (50) 23 (12)	18.34	1.1
Escobar-Morreale et al.[3]	Profile of Mood States	7.8 (7.4) 7.1 (8.9)	8.18	0.085
Levitt et al. (unpublished)	Inventory for Depressive Symptomatology	5.2 (2.7) 5.4 (3.1)	2.92	−0.06
Saravanan et al.[17]	Hospital Anxiety and Depression Scale, Depression subscale	4.6 (4.6) 4.7 (3.3)	3.99	−0.02
Siegmund et al.[14]	Profile of Mood States, Depression subscale	5.6 (2.2) 5.4 (2.7)	2.46	0.081
Sawka et al.[13]	Comprehensive Epidemiological Screening for Depression	12.8 (8.6) 14.4 (10.3)	9.50	−0.16
Walsh et al.[12]	General Health Questionnaire	18.3 (10.1) 21.2 (10.1)	10.05	−0.28

SD: standard deviation; effect size: Treatment (T4 + T3) minus Control (T4) subjects.

form a metaanalysis of all studies, using effect of treatment type on mood measures as the primary outcome. The meta-analysis confirmed no significant effect of treatment type on this outcome measure. Nonetheless, some unresolved issues still remain, particularly the preponderance of patient preference for combination therapy in those studies where it was measured. Given that dissatisfaction with levothyroxine therapy in a subset of treated patients is one of the major reasons behind research in this area, the gold standard of measuring success must, by necessity, be patient satisfaction. This global measure can be approximated, but not replicated, by the various psychological instruments used to date. Further study is required to elucidate why some patients prefer combination therapy and to clarify the discrepancy between patient preference and the lack of difference between treatment groups on objective measures of outcome. It is specifically because of this discrepancy that some experts in the field of thyroidology recommend a trial of additional T3 when a patient remains lethargic or complains of memory problems despite a normalized TSH on T4 replacement.[18] It also clarifies why research on combination therapy is ongoing, despite the recent series of negative articles. It is noteworthy that Appelhof and colleagues[17] have expanded research on T4/T3 therapy into the molecular level, investigating whether the preference they found for combination therapy in their earlier research could be explained by recently-elucidated polymorphisms in Type 2 deiodinase.[20] Type 2 deiodinase regulates conversion of T4 to T3 in the brain. The frequency of two polymorphisms was evaluated in 141 patients with autoimmune hypothyroidism who participated in a trial comparing T4/T3 combination therapy to T4-alone. No difference in the prevalence of the polymorphisms was found between patients who preferred combination therapy and those who did not.

A second confound affecting research on patient preference for combination therapy versus levothyroxine-alone is the inability to simulate the physiology of T3 production and metabolism by the body with our present pharmacological armamentarium. Present formulations of T3 result in erratic levels throughout the day and, therefore, are non-physiological. Hennemann et al.[21] recently developed a slow-release T3 and presented pharmacokinetic data revealing an absence of the T3 peaks seen with the T3 compounds presently on the market. They conclude that future studies of combination therapy should only be performed utilizing slow-release T3 preparations. Wartofsky,[22] in an accompanying editorial, notes that the pharmacodynamics of their compound exhibits a plateau between 2 and 6 hours, followed by declining levels at 9 hours, and is, therefore, not ideal, and that the chemical properties of the slow-release T3 were not published, thus precluding investigators' use of the slow-release T3 in patient-preference studies.

Although these data do not support the clinical adoption of combined treatment as standard therapy for hypothyroidism, the possibility of benefit in selected cases may be useful to consider. Moreover, further study may be required to elucidate the discrepancy between patient preference and the lack of difference between treatment groups on objective measures of outcome.

TABLE 3. Percentage Preference for Type of Thyroid Hormone Treatment in Four Crossover Studies

Study	No Preference	Preferred T4-Only	Preferred T4 + T3
Applehof et al.[16]	Not reported	14/48 (29.2) (5:1 dosage)	24/46 (52.2)
Bunevicus et. al.[10]	11/33 (33.3)	2/33 (0.06)	20/33 (60.6)
Walsh et. al.[12]	18/100 (18.0)	46/100 (46.0)	36/100 (36.0)
Escobar et. al.[3]	6/20 (30.0)	2/20 (10.0)	12/20 (60.0)
Total (with Applehof et al.[16])	35/153 (22.9)	64/201 (31.8)	92/199 (46.2)
Total (without Applehof et al.[16])	35/153 (22.9)	50/153 (32.7)	68/153 (44.4)

References

1. Singer PA, Cooper DS, Levy EG, et al: Treatment guidelines for patients with hyperthyroidism and hypothyroidism. JAMA 1995; 273:808–812
2. Stock JM, Surks MI, Oppenheimer JN: Replacement dosage of L-thyroxine in hypothyroidism: a re-evaluation. N Engl J Med 1974; 290:529–533
3. Escobar-Morreale HF, Botella-Carratero I, Gomez-Bueno M, et al: Thyroid hormone replacement therapy in primary hypothyroidism: a randomized trial comparing L-thyroxine plus liothyronine with L-thyroxine alone. Arch Intern Med 2005; 142:412–424
4. Saravanan P, Chau W-F, Roberts N, et al: Psychological well-being in patients on "adequate" doses of L-thyroxine: results of a large, controlled, community-based questionnaire. Clin Endocrinol 2002; 57:577–585

5. Joffe RT, Sokolov SH: Thyroid hormone treatment of primary unipolar depression: a review. Int J Neuropsychopharmacol 2000; 3:143–147
6. Baumgartner A: Thyroxine and the treatment of affective disorders: an overview of the results of basic and clinical research. Int J Neuropsychopharmacol 2000; 3:149–165
7. Cooper DS: Combined T4 and T3 therapy: back to the drawing board (editorial). JAMA 2003; 290:3002–3004
8. Walsh JP: Dissatisfaction with thyroxine therapy: could the patients be right? Curr Opin Pharmacol 2002; 2:717–722
9. Canaris GJ, Manowitz NR, Mayor G, et al: The Colorado Thyroid Disease Prevalence Study. Arch Intern Med 2000; 160:526–534
10. Bunevicius R, Kazanavicius G, Zalinkevicius R, et al: Effects of thyroxine as compared with thyroxine-plus-triiodothyronine in patients with hypothyroidism. N Engl J Med 1999; 340:424–429
11. Clyde PW, Harari AE, Getka EJ, et al: Combined levothyroxine-plus-liothyronine compared with levothyroxine-alone in hypothyroidism: a randomized, controlled trial. JAMA 2003; 290:2952–2958
12. Walsh JP, Shiels L, Lim EM, et al: Combined thyroxine/liothyronine treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine-alone: a randomized, controlled trial in patients with primary hypothyroidism. J Clin Endocrinol Metab 2003; 88:4543–3550
13. Sawka AM, Gerstein HC, Marriott MJ, et al: Does a combination regimen of thyroxine (T4) and 3,5,3′-triiodothyronine improve depressive symptoms better than T4-alone in patients with hypothyroidism? results of a double-blind, randomized trial. J Clin Endocrinol Metab 2003; 88:4551–4555
14. Siegmund W, Spieker K, Weike AI, et al: Replacement therapy with levothyroxine-plus-triiodothyronine (bioavailable molar ratio 14:1) is not superior to thyroxine-alone to improve well-being and cognitive performance in hypothyroidism. Clin Endocrinol 2004; 60:750–757
15. Escobar-Morreale HF, Botella-Carratero JI, Escobar Del Ray F, et al: Review: treatment of hypothyroidism with combinations of levothyroxine and liothyronine. J Clin Endocrinol Metab 2005; 90:4046–4954
16. Appelhof BC, Fliers E, Wekking EM, et al: Combined therapy with levothyroxine and liothyronine in two ratios, compared with levothyroxine monotherapy in primary hypothyroidism: a double-blind, randomized, controlled clinical trial. J Clin Endocrinol Metab 2005; 90:2666–2674
17. Applehof BC, Peeters RP, Wiersinga WM, et al: Polymorphisms in Type 2 deiodinase are not associated with well-being, neurocognitive functioning, and preference for combined thyroxine/3,5,3′-triiodothyronine therapy. J Clin Endocrinol Metab 2005; 90:6296–6299
18. Saravanan P, Simmons DJ, Greenwood R, et al: Partial substitution of thyroxine (T4) with triiodothyronine in patients on T4 replacement therapy: results of a large, community-based, randomized, controlled trial. J Clin Endocrinol Metab 2005; 90:805–812
19. Fleiss JL: The statistical basis of meta-analysis. Statistical Methods in Medical Research 1993; 2:121–145
20. Klein I: T3 and T4: are we missing half the picture? Clinical Cornerstone 2005; 7:S5–S7
21. Hennemann G, Cocter R, Visser TJ, et al: Thyroxine plus low-dose, slow-release triiodothyronine replacement in hypothyroidism: proof of principle. Thyroid 2004; 14:271–275
22. Wartofsky L: Combined levotriiodothyronine and levothyroxine therapy for hypothyroidism: are we a step closer to the magic formula? Thyroid 2004; 14:247–248